Revisiting occult cancer screening in patients with unprovoked venous thromboembolism

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Objectives

- Review the prevalence of occult cancer detection in patients with venous thromboembolism (VTE)
- Discuss the pros and cons of occult cancer screening in patients with unprovoked VTE
- Review the literature regarding the efficacy of limited and extensive occult malignancy screening strategies
- Discuss on-going and future studies on occult cancer screening in this patient population

Occult cancer detection

- **Prevalence**
- **Type of screening**
- **Clinical practice guidelines**

- **Prevalence**
- **Type of screening**
- **Clinical guidance**

- **Risk stratification**
- **On-going studies**
- **Biomarkers**

Past

- **Prevalence**
- **Type of screening**
- **Clinical practice guidelines**

- Prevalence
- Type of screening
- Clinical guidance

- Risk stratification
- On-going studies
- Biomarkers

Professor Armand Trousseau

Prevalence of occult cancer detection in patients with VTE

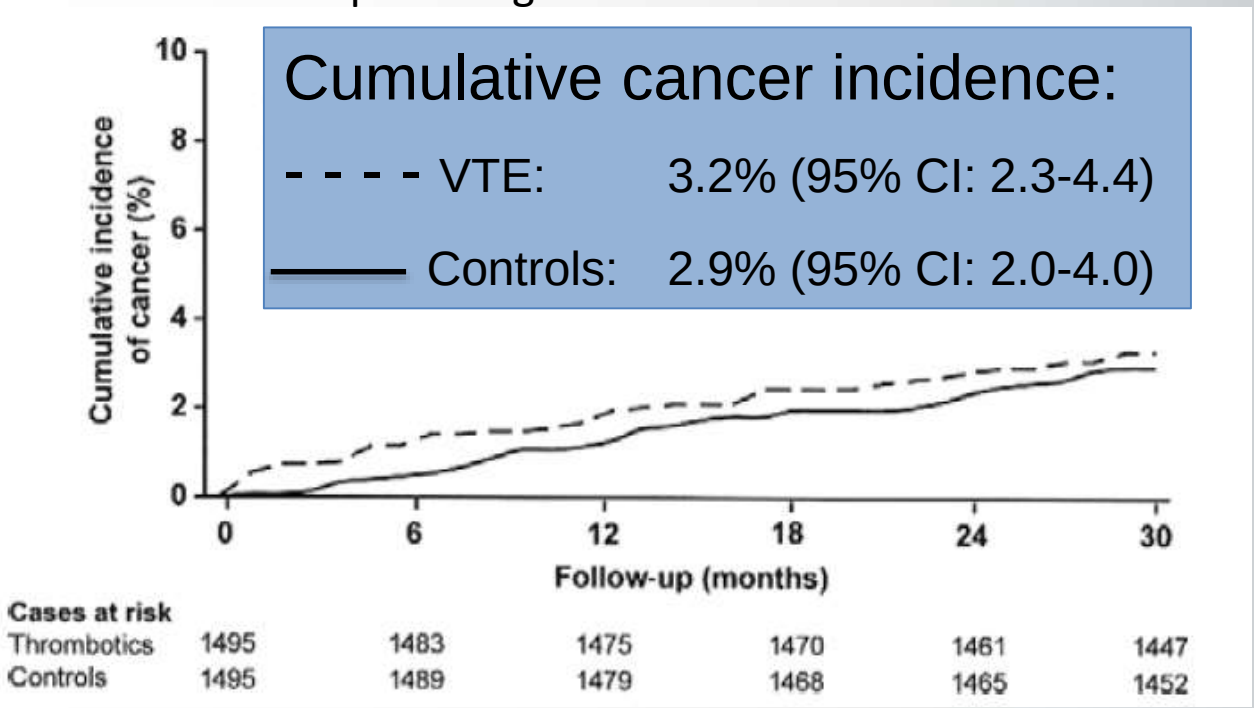
Baseline	Period Prevalence
Overall	4.1 (95% CI: 3.6-4.6)
Provoked	1.9 (95% CI: 1.3-2.5)
Unprovoked	6.1 (95% CI: 5.0-7.1**)**
After 12 months	
Overall	6.3 (95% CI: 5.6-6.9)
Provoked	2.6 (95% CI: 1.6-3.6)
Unprovoked	**10.0 (95% CI: 8.6-11.3)**

9,516 patients with VTE = 3,286 unprovoked; 3,297 provoked; 2,933 not specified

Carrier M et al. Ann Intern Med 2008;149:323-333

Long-term incidence of occult cancer

- Case-control study
- 1495 patients with symptomatic VTE
  - 55% unprovoked
  - 30 months follow-up starting 6 months after VTE



Prandoni P. J Thromb Hamost. 2010 May;8(5):1126-7.

Occult cancer screening in VTE patients

Why?

- Earlier detection
  - Curable cancer
  - ↑ survival
  - ↓ morbidity
- Treatment VTE

Why not?

- Anxiety
- May lead to unnecessary invasive procedures
  - "incidental findings"
- Costs

Types of screening strategies

- Limited cancer screening strategy
  - History, physical examination, basic blood work and CXR
- Extensive cancer screening strategy
  - As above in combination with:
    - CT abdomen/pelvis
    - U/S abdomen/pelvis
    - Tumor markers (PSA, CEA, CA-125)
    - PET scan

Limited screening strategy

- Limited screening is adequate to detect 90% of occult cancers
  - History
  - Physical exam
  - Routine blood work
    - CBC, electrolytes, BUN, creatinine, LFTs
  - CXR
  - +/- Urine analysis

Monreal M et al. Chest 1993;103:816-819
Monreal M et al. Cancer 1991;67:541-545
Bastounis EA et al. J Intern Med 1996;239:153-156
Cailleux N et al. J Mal Vasc 1997;22:322-325.

SOMIT trial

- 201 eligible patients (20% of expected number)
- Patients with negative limited screening were randomized (Zelen)
  - Observation
  - Extensive screening
    - U/S and CT abdomen/pelvis, gastroscopy, colonoscopy, hemoccult, sputum cytology, Tumor markers, pap smear and mammogram

Piccioli A et al. J Thromb Haemost 2004 Jun;2(6):884-9.

SOMIT trial

- Occult cancer detection
  - Extensive screening:
    - 13/99 (13.1%) occult malignancies detected
    - 1/99 (1%) missed
  - Observation:
    - 10/102 (9.8%) missed

- Earlier-stage cancers ($T_{1\text{-}2}N_0$)
    - 64% vs. 20%; p=0.047

- Cancer-related mortality
    - 4/102 (3.9%) vs. 2/99 (2.0%); p=NS

Piccioli A et al. J Thromb Haemost 2004 Jun;2(6):884-9.

Bottom line for the SOMIT trial

- Limited screening strategy alone is insufficient to detect all occult cancers
- Still unclear if extensive screening offers a beneficial effect on prognosis (mortality, morbidity, QALY)
  - Non-significant trend in survival advantage
    - Inadequate power due to small sample size vs. no true difference in survival between groups
  - Trial stopped early
    - Potential selection bias
  - ? Generalizability

Incremental value of extensive screening strategy

Diagnostic modality	Limited screening	Extensive screening
CT abdomen/pelvis	49.4 (95% CI: 40.2-58.5)	69.7 (95% CI: 61.1-77.8)
US abdomen/pelvis	54.2 (95% CI: 45.5-65.9)	63.5 (95% CI: 54.9-72.1)
Tumor marker CEA	66.7 (95% CI: 28.9-100)	83.7 (95% CI: 53.8-100)
Tumor marker PSA	51.0 (95% CI: 40.0-62.0)	60.6 (95% CI: 49.6-71.7)

Carrier M et al. Ann Intern Med 2008;149:323-333

Guidelines

ACCP

- Does not provide specific occult malignancy screening recommendations.

NICE

- All patients diagnosed with unprovoked VTE should be offered a limited screening strategy and in those patients aged over 40 a CT abdomen/pelvis, and mammography for women, is also suggested.

Chest 2012;141:e419S-e494S; Acute Med 2012;11:138-42.

Take home messages from the past…

- The prevalence of occult cancer in patients with a unprovoked VTE is 10%

- The risk of occult cancer is similar to the general population after the initial 6 to 12 months of follow-up

- Occult cancer screening using CT abdomen might be reasonable in high risk patients

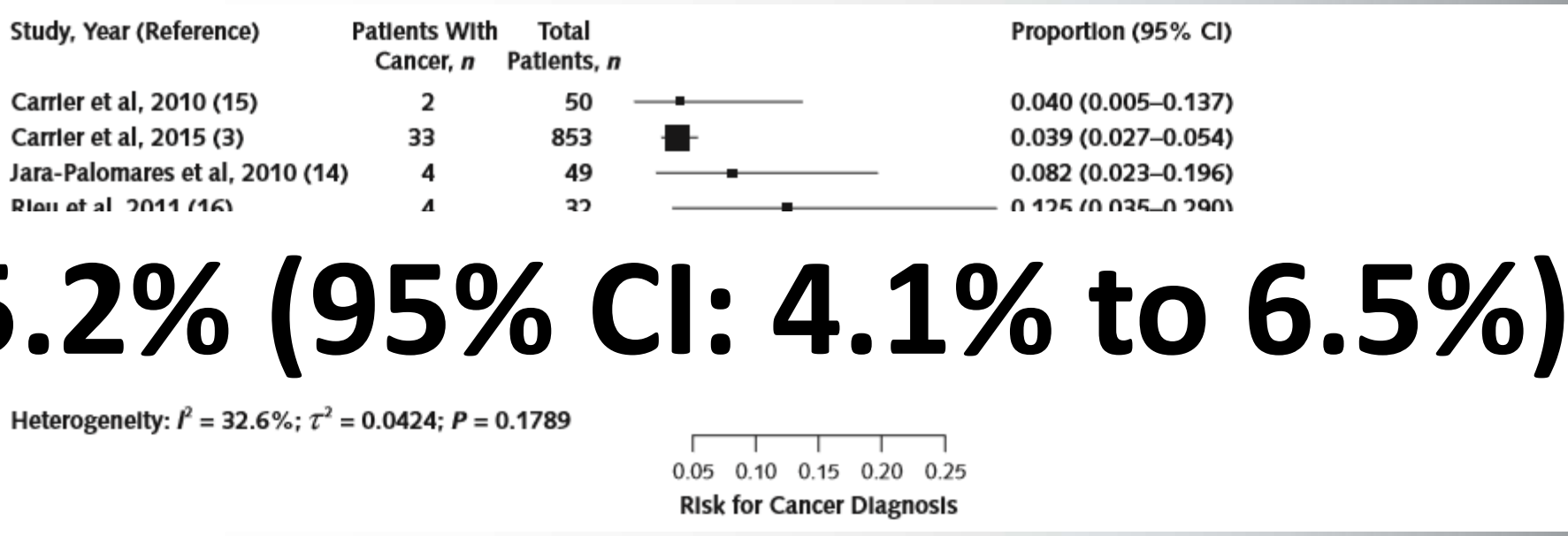
Present

- Prevalence
- Type of screening
- Clinical practice guidelines

- **Prevalence**
- **Type of screening**
- **Clinical guidance**

- Risk stratification
- On-going studies
- Biomarkers

12-month period prevalence

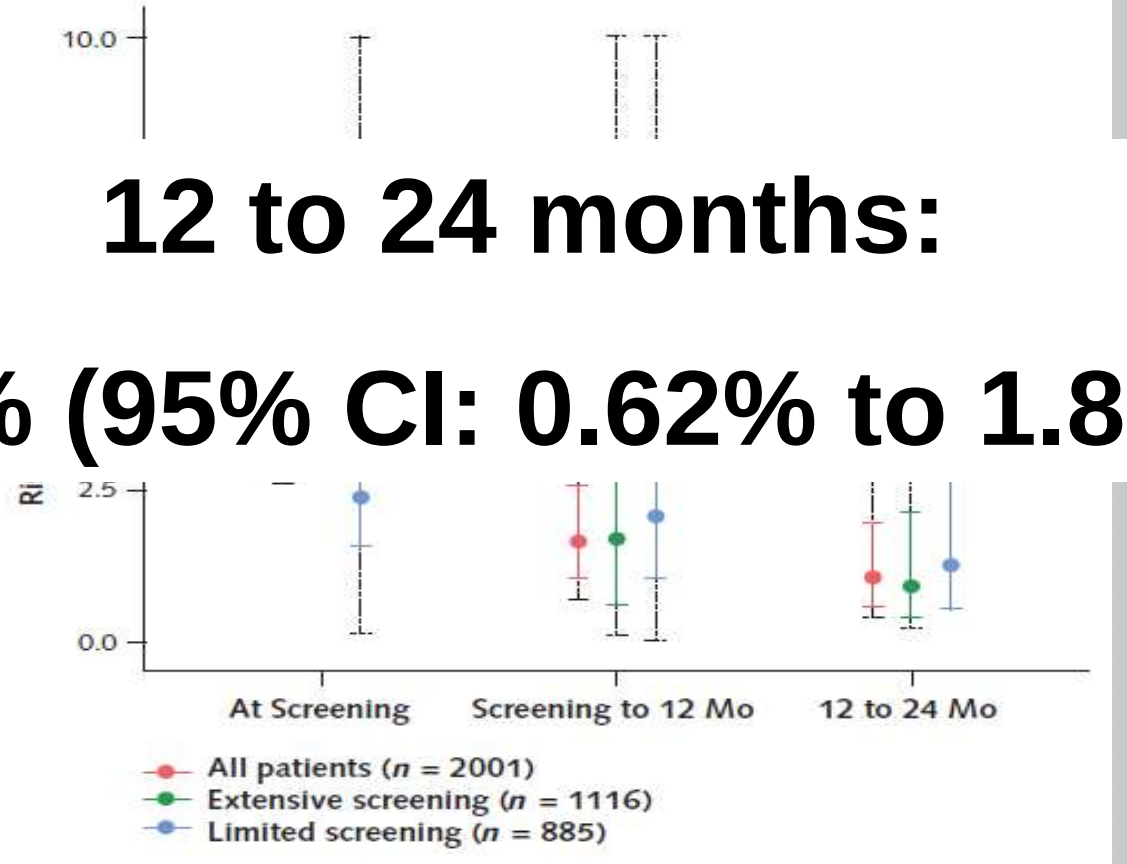


5.2% (95% CI: 4.1% to 6.5%)

Van Es N et al. Ann Intern Med. 2017 Sep 19;167(6):410-417.

Long-term prevalence of occult cancer

Figure 3. Period prevalence of cancer, according to time points.



12 to 24 months:

1.1% (95% CI: 0.62% to 1.8%)

Van Es N et al. Ann Intern Med. 2017 Sep 19;167(6):410-417.

Unknowns about occult cancer screening strategies

- Unknown if extensive screening improves survival or cancer-related morbidity or quality of life
  - Lead time bias
  - Length-time bias
- Radiation exposure
  - CT abdomen/pelvis with contrast
    =234 CXR or 34 mammograms
- Clinical impact and cost associated with false-positive findings (“incidentoloma”)

Smith-Bindman R et al. Arch Intern Med. 2009;169(22):2078-2086.


I FOUND A LUMP...
UNNECESSARY CANCER SCREENING
COST OF HEALTH CARE
THE BUFFALO NEWS
CAGLECARTOONS.COM
©2009 ADAM ZYGLIS

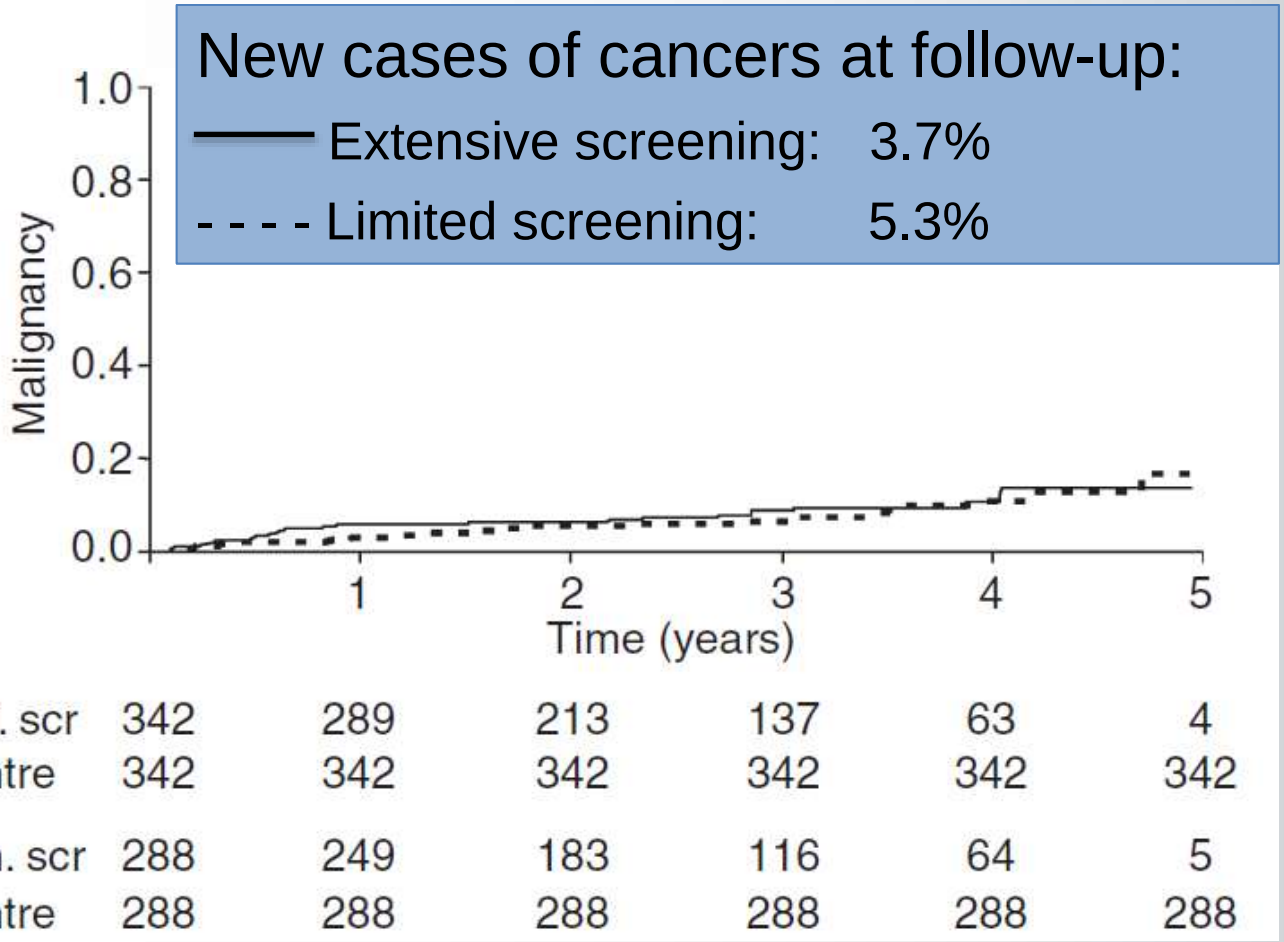
Trousseau study

- 630 patients with unprovoked VTE
- Not randomized but center-specific
  - Limited screening (n=288): Hx, physical examination, blood work, CXR
  - Extensive screening (n=342): CT chest/abdomen + mammogram

van Doormaal et al. J thromb Haemost 2011 Jan;9(1):79-84.

Trousseau study

- No difference in overall mortality was observed



van Doormaal et al. J thromb Haemost 2011 Jan;9(1):79-84.

SOME trial

- 854 patients with unprovoked VTE
- Randomized to:
  - **Limited occult cancer screening:**
    - basic blood work, chest X-ray and breast/cervical/prostate cancer screening
  - **Limited cancer screening + comprehensive CT abdomen/pelvis**
    - including a virtual colonoscopy and gastroscopy;
    - a biphasic enhanced CT of the liver;
    - a parenchymal pancreatogram;
    - and an uniphasic enhanced CT of the distended bladder

Carrier M et al. N Engl J Med. 2015;373:697-704

SOME trial

- Missed cancers
  - 4/431 (0.93%) *vs.* 5/423 (1.18%)
    - Absolute difference: 0.25% (95% CI: -1.1% to +1.6%)
- No difference in total occult cancer detection
  - 3.2 *vs.* 4.5%
- No difference in early cancers, overall survival or cancer-related survival

Carrier M et al. N Engl J Med. 2015;373:697-704

D'Acquapendente trial

- 195 cancer-free patients
  - Limited vs. CT thorax/abdomen/pelvis
- Occult cancer detection
  - 8/97 (8%) *vs.* 10/98 (10%)
    - 2% (95% CI: -7 to 11%; p=0.81)
- Missed cancers
  - 2% in each group
- No difference in overall or cancer-related survival

Piccioli A, et al. Semin Thromb Hemost 2016;42:884-90.

MVTEP trial

- 494 patients with unprovoked VTE
- Randomized to:
  - **Limited occult cancer screening:**
    - basic blood work, chest X-ray and breast/cervical/prostate cancer screening
  - **Limited cancer screening + FDG PET/CT**

Robin et al. Lancet Oncol. 2016 Feb;17(2):193-9.

MVTEP trial

- Occult cancer detection
  - 4/197 (2.0%) *vs.* 11/197 (5.6%)
    - Absolute difference of 3.6% (95% CI: 0.4 to 7.9%; p=0.065)
- Missed cancers
  - 4.7% *vs.* 0.5%
    - Absolute risk difference of 4.1% (95% CI: 0.8 to 8.4%)
- No difference in early cancers, overall survival or cancer-related survival

Robin et al. Lancet Oncol. 2016 Feb;17(2):193-9.

ISTH Guidance

- Patients with unprovoked VTE should only undergo a limited cancer screening including:
  - Medical history and physical examination
  - Laboratory investigations and urinalysis
  - chest X-ray
  - Age and gender- specific cancer screening
    - breast, cervical, colon, and prostate
- Further clinical trials are required to assess the risks and benefits of an extensive occult cancer screening program in high risk patients.

Delluc A et al. J Thromb Haemost. 2017 Oct;15(10):2076-2079

Take home message

- The prevalence of occult cancer in patients with a unprovoked VTE seems to be lower (~5%) than previously reported (10%)

- Patients with unprovoked VTE should only undergo a limited cancer screening including basic blood work and age and gender-specific cancer screening

The Future

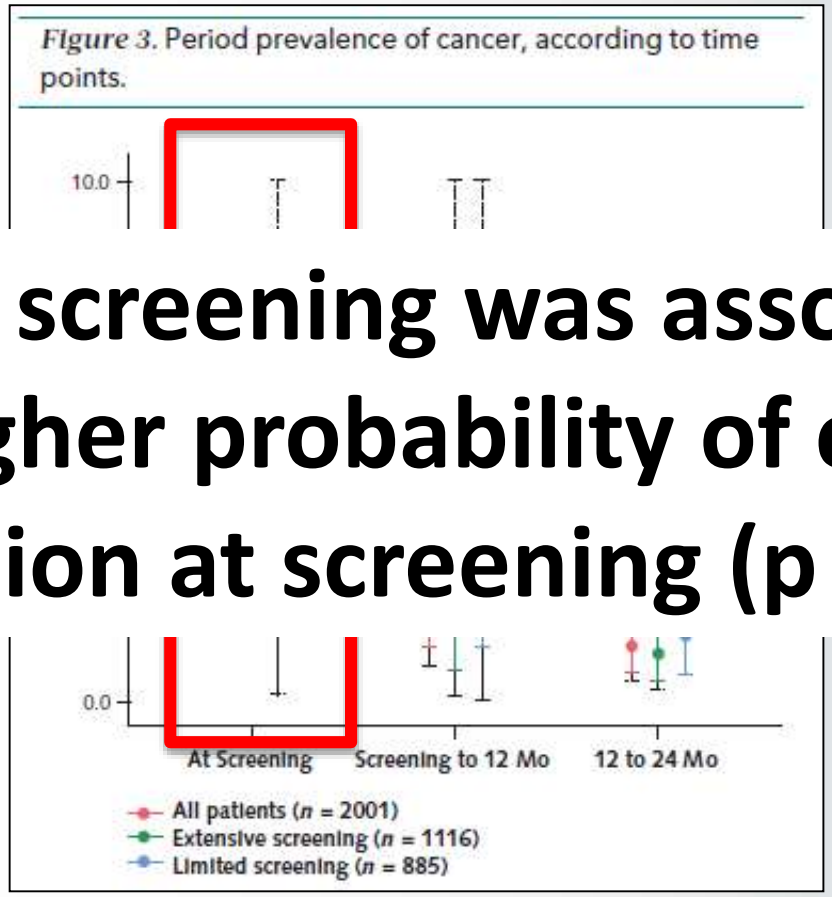
- Prevalence
- Type of screening
- Clinical practice guidelines

- Prevalence
- Type of screening
- Clinical guidance

- **Risk stratification**
- **On-going studies**
- **Biomarkers**


”We need more clinical trials…”

Limited or extensive screening in high risk subgroups?

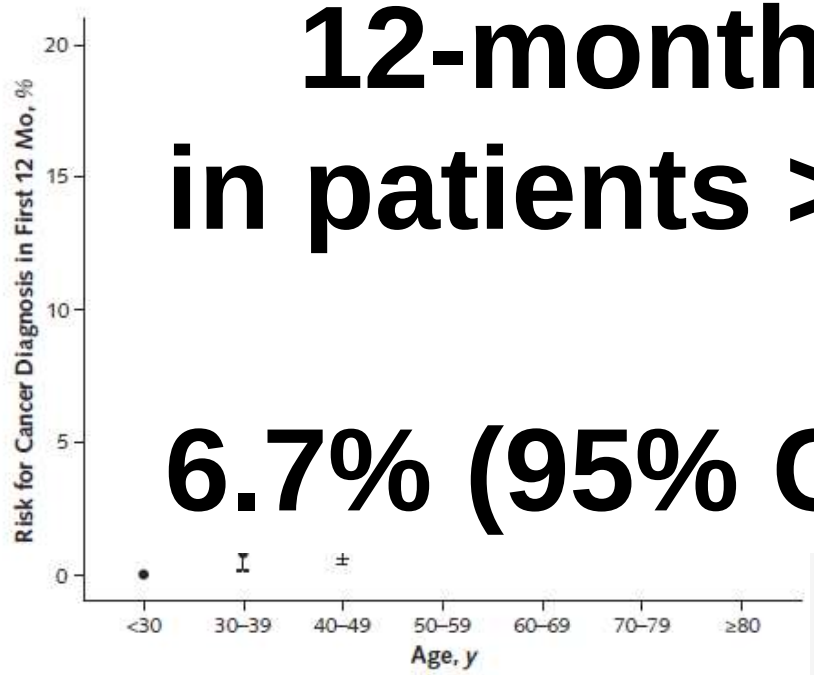


Extensive screening was associated with a 2-fold higher probability of occult cancer detection at screening (p = 0.012)

Van Es N et al. Ann Intern Med. 2017 Sep 19;167(6):410-417.

High-risk subgroup of patients with unprovoked VTE?

Figure 4. Point prevalence of cancer at 12 months, stratified by age cohorts.



12-month prevalence in patients > 50 years old:

6.7% (95% CI: 5.5 to 8.2%)

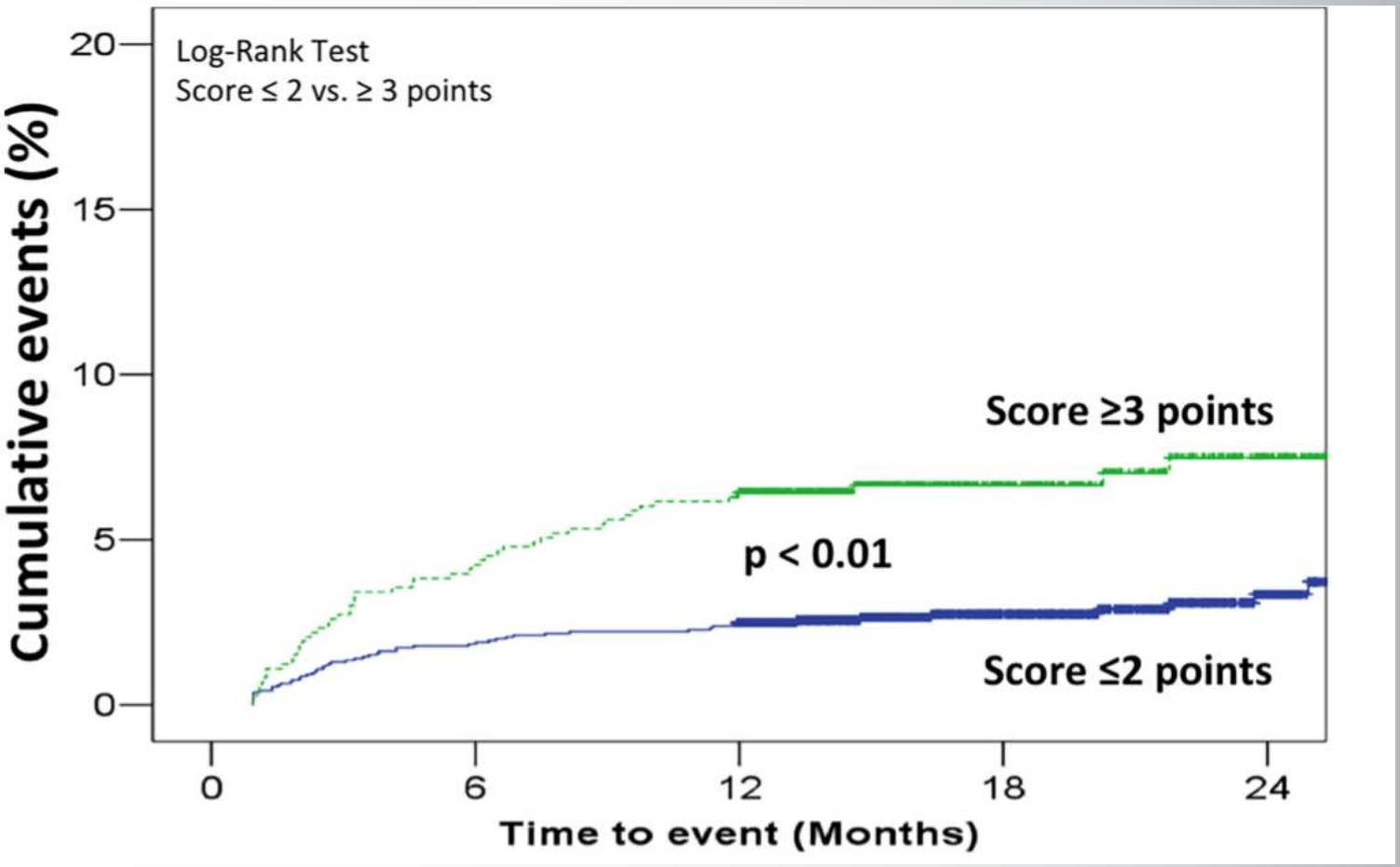
Van Es N et al. Ann Intern Med. 2017 Sep 19;167(6):410-417.

High-risk subgroup of patients with VTE?

Variable	β Coefficient	OR	95% Confidence Limits		*P* Value	Points
			Lower	Upper		
Male sex	0.378	1.46	1.19	1.79	< .001	+1
Age > 70 y	0.642	1.90	1.55	2.33	< .001	+2
Underlying conditions						
Chronic lung disease	0.338	1.40	1.07	1.84	.015	+1
Anemia	0.539	1.71	1.38	2.13	< .001	+2
Platelet count ≥ 350 × 10^6/mm^3	0.334	1.40	1.03	1.90	.034	+1
Risk factors for VTE						
Postoperative status	−0.722	0.49	0.32	0.73	< .001	−2
Prior VTE	−0.392	0.68	0.51	0.89	.006	−1

Jara-Palomares J et al CHEST 2017; 151(3):564-571

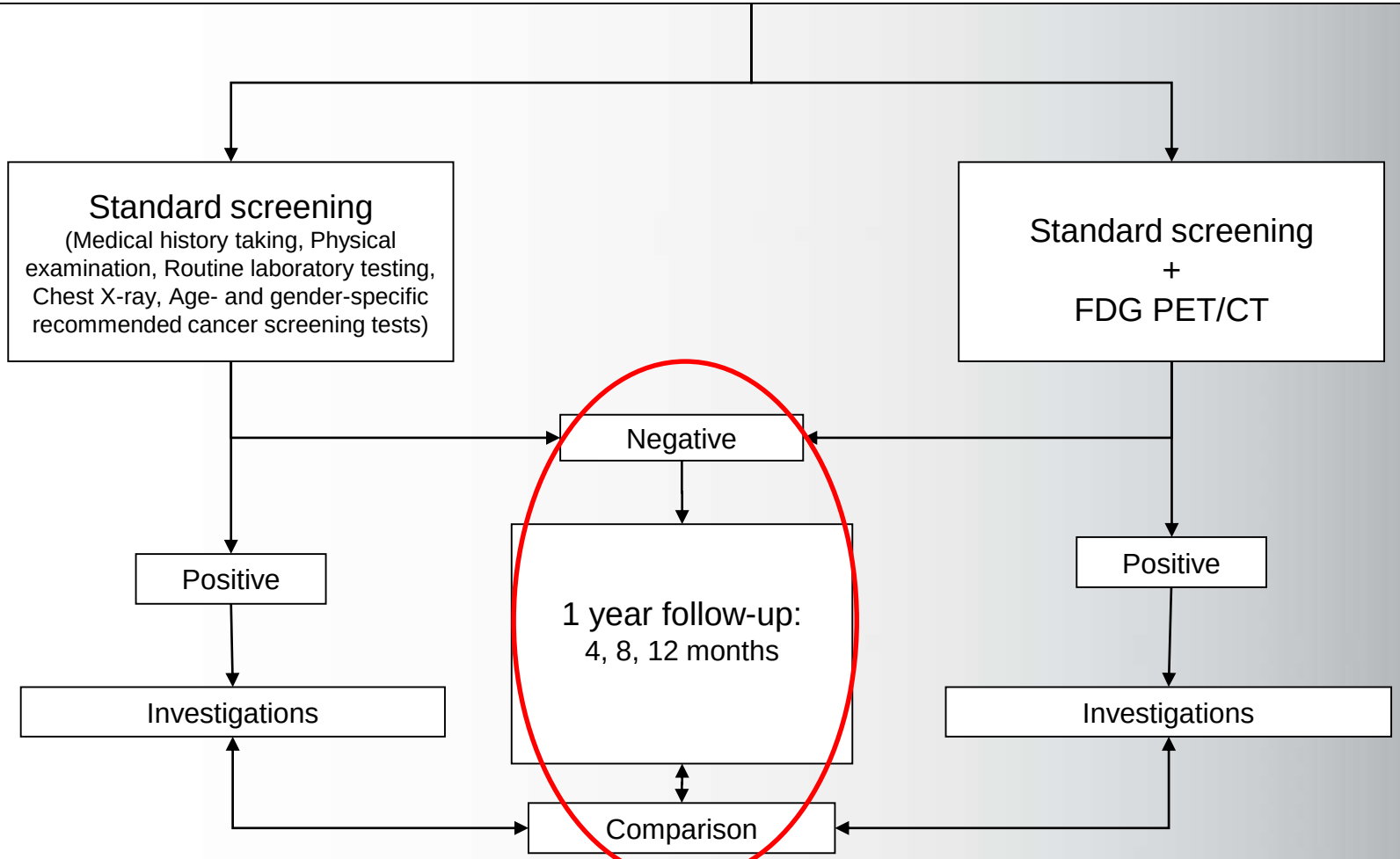
Validation of the predictive score



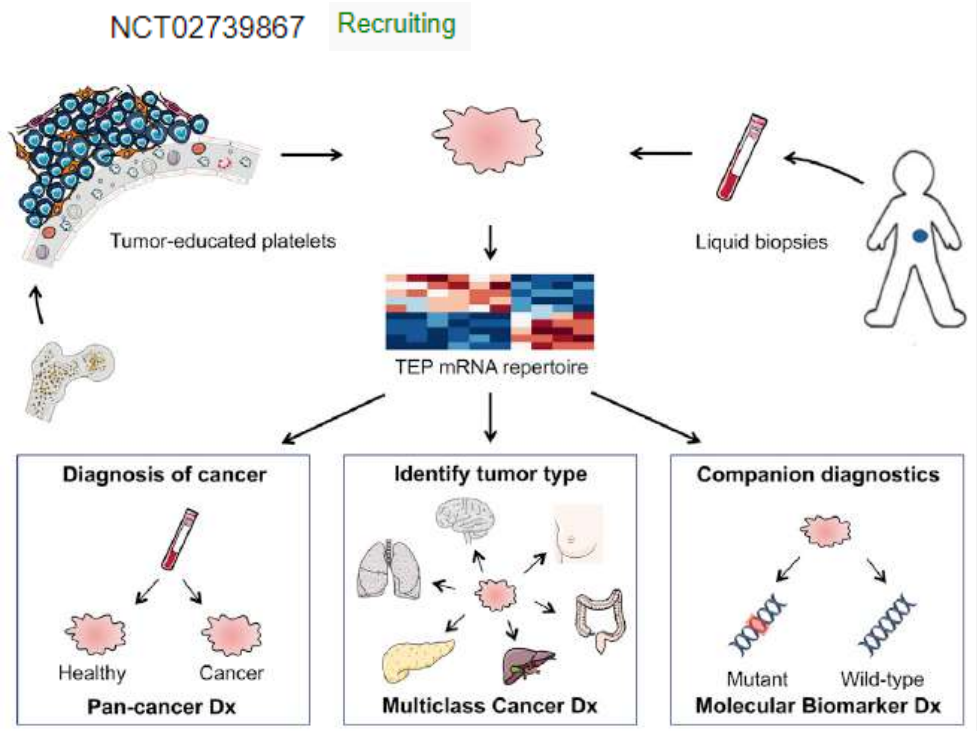
Jara-Palomares J et al PLoS ONE 2018;13(3):e0194673.

MVTEP 2

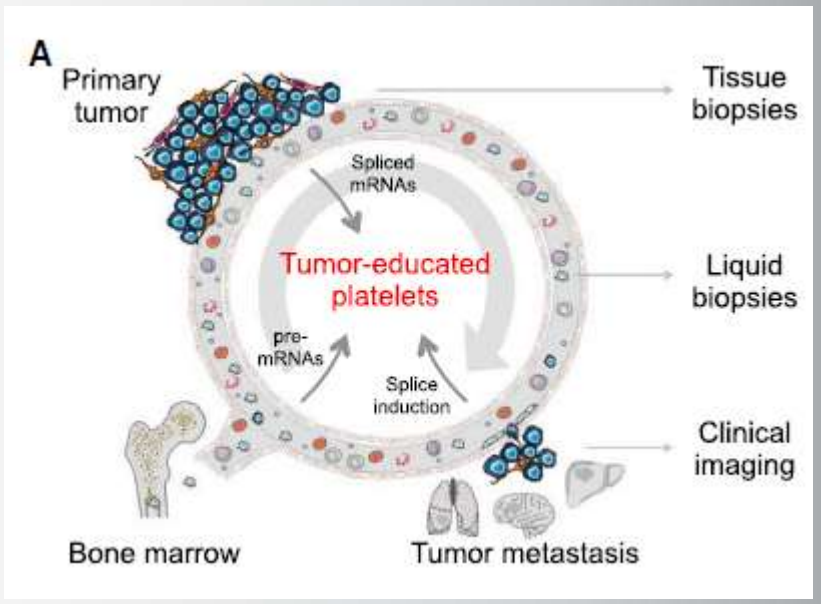
Inclusion criteria: Age **≥ 50 years** + Unprovoked VTE (DVT or PE)
Exclusion criteria: Unable or unwilling to consent,
Active malignancy (known malignancy, evolutive and/or treated during the last 5 years),
VTE provoked by a major inherited or acquired risk factor.



PLATO-VTE: Tumor-educated platelets in VTE



Best, Cancer Cell 2015



- RNA profiling of platelets

- Patients ≥ 40y
- First episode of unprovoked VTE
- Primary outcome: Solid ou hematological cancer
- 462 patients
- Estimated completion date: March 2019

Take home messages

- Prevalence of occult cancer is low in patients with first unprovoked VTE
  - **But** clinicians should maintain a low-threshold of suspicion for cancer
- Routine screening with comprehensive CT abdomen/pelvis does not provide a clinically significant benefit
- Awaiting results of MVTEP-2 and PLATO-VTE Study!!


... I WONDER IF THEY HAVE A DRIVE-THRU OPTION?
PERFECTLY HEALTHY BUT WORRIED ABOUT CANCER?
HEAD-TO-TOE CANCER SCREENING
NEXT EXIT
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Thank you

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